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Insert Abstract Below

DEFINING DOSE ACROSS DIFFERENT EXPERIMENTAL DESIGNS: FIBER EQUIVALENT DIAMETER AND SURFACE AREA

Inhaled fibers (elongated bio-durable particles) of all lengths have been shown to induce pathological responses, but different sizes are respirable in different species. To be able to accurately assess the health effects observed in toxicological or epidemiological studies, comparative potency must be assessed as a function of both the respirable and retained fractions of inhaled fibers for *in-vivo* and *in-vitro* studies, and comparative doses translated to human equivalent air exposures. In this paper we explore new techniques to translate and compare the respirable and retained fractions for different experimental designs across species. We also define and discuss relevant dose metrics based on mode of action considerations.

The preparation of an appropriate respirable fiber test sample is a critical and challenging first step of toxicological studies. Traditionally, approaches to size selection have been based on particle aerodynamic diameter and the use of centrifuges or cyclones which separate by coriolis or centrifugal forces. Unlike particles, fibers cannot be simply described by a single diameter since both length and width determine their aerodynamic properties, so such separation techniques cannot be extended to fibers without proper modifications. Further, sedimentation is the basis for settling velocity whereas examination of fiber transport mechanisms shows that the ability of fibers to enter the respiratory tract is determined by inertial properties. Thus, an equivalent fiber diameter for impaction needs to be defined and used as the basis for size selection. We first calculate a particle impaction diameter to show the difference in respirable estimates based on mechanism. We then show the fiber equivalent impaction diameter, assuming a random orientation as a function of fiber diameter and aspect ratio. We further illustrate the influence of using a bivariate distribution function rather than the aspect ratio to characterize the fiber size based on a range of fiber parameters for the joint correlation between length and diameter distributions. Once inhaled, the size and shape distributions for fibers retained in different respiratory regions continue to be critical determinants of relative potency for lung disease. The principal determinants of potency for different internal dose metrics are persistence, effective total fiber surface area, and particle surface ability to elicit reactive chemical species. These determinants also apply to pleural diseases, including mesothelioma, as well as potential endpoints in extrapulmonary tissues. The impact on dose estimates for various toxicological studies is depicted, and correction factors derived to compensate for these considerations across experimental designs. (These views do not represent US EPA policy).

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